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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SEP 4 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Folpet

FROM: Esther Rinde, Ph.D. E. Rinde 8/6/86
Scientific Mission Support Staff
Toxicology Branch/HED (TS-769c)

TO: Henry Jacoby
Product Manager #21
Registration Division (TS-767c)

The Toxicology Branch Peer Review Committee met on July 14, 1986 to discuss and evaluate the weight-of-the-evidence on Folpet, with particular reference to its oncogenic potential.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with peer review unless otherwise stated).

Theodore M. Farber — Theodore M. Farber

William L. Burnam — Wm L Burnam

Reto Engler — Reto Engler

Louis Kasza — Louis Kasza

Bertram Litt/R. Levy/H. Lacayo — B. Litt

Robert Beliles — Robert Beliles

John A. Quest — John A. Quest

Esther Rinde — Esther Rinde

2. Scientific Reviewers: (Non-panel members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Stephen Saunders (Reviewer-Folpet) D. Stephen Saunders

Marion Copley (Reviewer-Captan) Marion Copley

Larry Chitlik/W. Teeters (Section Head) W. Teeters

3. Peer review members in absentia: (Committee members who were not able to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Richard Hill/Don Barnes Did not read

Stephen Johnson

Anne Barton

Diane Beal

Judith Hauswirth

B. Material Reviewed:

The material available for review consisted of the following:

° Two Year Feeding Study in Rats (Chevron) Project #23107-109

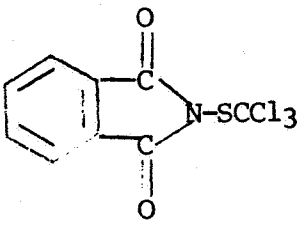
° Two Year Feeding Study in Rats (Makhteshim) Study #MAK/022/FOL

° Lifetime Oncogenic Feeding Study in Mice (Chevron) Socal Study #1331

° Lifetime Oncogenic Feeding Study in Mice (Makhteshim) Study #MAK/015/FOL

C. Background Information:

Folpet (N-[trichloromethyl]thiophthalimide) is a fungicide that is similar in structure to the fungicides captan and captafol, which have been demonstrated to be oncogenic in rats and mice. Folpet is currently registered for a variety of food uses, and is contained in a number of house-hold products.



FOLPET

V

D. Evaluation of Oncogenicity Evidence for Folpet:

1. Two Year Feeding Study in Rats (Chevron)

Folpet was fed in the diet to 60 male and 60 female Charles River CD Sprague-Dawley rats at 0, 200, 800 and 3200 ppm (nominal concentrations) for 104 weeks, with interim sacrifice at 52 weeks of 10/sex/dose. The study was conducted at Hazleton Labs., VA.

At terminal sacrifice, treatment-related increases in the incidence* of hyperkeratosis/acanthosis of the stomach were noted in mid and high dose males and females. This finding seemed to be associated with an increased incidence of erosion/ulceration in high dose rats.

Possible treatment-related increases in the incidences* of adenoma/carcinoma of the thyroid and interstitial cell tumor of the testes were noted in treated males (Table 1). In the case of the thyroid, a dose-related trend for the increase in incidence of C-cell carcinoma ($p=0.05$) was noted. The combined incidence of adenoma and carcinoma (in the low dose group only) was $p=0.05$.

Historical control data have been requested but not received from Hazleton. Pending arrival of the Hazleton data, representative data from in-house literature, on the incidence of thyroid C-cell and interstitial cell tumors in Sprague-Dawley rats, was used:

The incidence of C-cell carcinoma in treated rats (at the high dose) is below or slightly above (if interim sacrifice animals are censored out) that in historical controls. The incidences of other tumor types (thyroid adenoma, testicular interstitial) are within the range of historical controls.

MTD is an issue in this study, since although there was a clear effect on the stomach (edema, inflammation, erosion/ulceration in high dose animals), no alterations in body weight or food consumption were observed. The Committee felt that since the hyperkeratosis/acanthosis** seen in this study, were also seen in the Makhteshim mouse study - along with neoplasia, tumors may also have arisen in this study at a higher test dose.

When the historical control data from Hazleton are received, this study will be reevaluated and there may be additional concerns raised for the thyroid and testicular effects. However, even if these concerns are assuaged by comparison with in-house historical controls, the more serious concern regarding the "preconditional lesions" of the stomach will remain.

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*Compared to concurrent controls

**Hyperkeratosis/acanthosis could be "preconditional lesions" for neoplasia [L.Kasza].

Chevron 2 yr rat feeding

Table 1 Selected Neoplastic Findings[a]

Lesion	Sacrifice	DOSE GROUPS (PPM) MALES 0	200	800	3200	FEMALES 0	200	800	3200
THYROID									
C-cell Hyperplasia	1yr Int.	0/10	0/10	0/10	0/10	1/10	1/10	0/10	1/10
	DOT/MS	0/27	0/13	1/18	2/19	4/19	2/21	0/19	2/20
	Final	3/23	6/37	3/32	6/31	9/31	9/29	8/31	3/30
	TOTAL	3/60	6/60 10% (12%)	4/60 6.7% (8%)	8/60 13.3% (16%)	14/60	12/60	8/60	6/60
C-cell Adenoma	1yr Int.	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	DOT/MS	0/27	1/13	0/18	1/19	2/19	0/21	1/19	1/20
	Final	0/23	7/37	2/32	1/31	2/31	4/29	2/31	1/30
	TOTAL	0/60	8/60 13.3% (16%)	2/60 3.3% (4%)	2/60 3.3% (4%)	4/60	4/60	3/60	2/60
C-cell Carcinoma	1yr Int.	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
	DOT/MS	1/27	0/13	0/18	1/19	0/19	0/21	2/19	0/20
	Final	0/23	1/37	2/32	3/31	1/31	1/29	1/31	0/30
	TOTAL	1/60	1/60 1.6% (2%)	2/60 3.3% (4%)	4/60 6.7% (8%)	1/60	1/60	3/60	0/60
Adenoma + Carcinoma	TOTAL	1/60	9/60 15% (18%)	4/60 6.7% (8%)	6/60 10% (12%)	3/60	5/60	3/60	1/60
TESTES									
Interstitial Cell Hyperplasia	1yr Int.	0/10	0/10	2/10	1/10				
	DOT/MS	0/27	0/12	1/17	1/19				
	Final	2/23	10/37	8/32	7/31				
	TOTAL	2/60	10/60 16.7% (20%)	11/60 18.3% (22%)	9/60 15% (18%)				
Interstitial Cell Tumor	1yr Int.	0/10	0/10	0/10	0/10				
	DOT/MS	0/27	0/12	1/17	2/19				
	Final	1/23	5/37	3/32	6/31				
	TOTAL	1/60	5/60 8.3% (10%)	4/60 6.7% (8%)	8/60 13.3% (16%)				

[a]data excerpted from submitted study. 1yr Int = 1 year interim sacrifice; DOT/MS = Died on test/Moribund sacrifice; Final = terminal sacrifice.

(28 Groups 14 Studied)

HISTORICAL CONTROLS

MALES

C-cell Adenoma: 4.3% (0-15.6%)

C-cell Carcinoma: 2.3% (0-7.5%)

Interstitial Cell: 8.5% (0-24.6%)

2. Two Year Feeding Study in Rats (Makhteshim)

Folpet was fed in the diet to 60 male and 60 female Charles River Fischer 344 rats at 0, 500, 1000, and 2000 (nominal concentrations). This study was conducted at Life Science Research, Israel.

The formal review of this study could not be completed by the Reviewer prior to the Peer Review Meeting, owing to its recent submission. The Registrant, however reported findings of statistically significant increases in tumor incidences (Table 2). According to the life-table analysis by the Registrant, there were significant increases* ($p<0.05$) in C-cell adenomas in high dose females (but not in males). (Statistically significant increases* in benign fibroepithelial tumors of the mammary gland and in malignant lymphomas - only when males and females were combined were also reported.)

The incidence of C-cell hyperplasia of the thyroid was increased* in low and mid-dose males, however the Registrant did not perform histopathology on all of the low and mid-dose animals.

MTD: This study had not yet been reviewed in sufficient depth to allow for the assessment of the adequacy of dose levels. It was noted, however, that the highest dose in this study was below the highest dose in the study discussed in the preceding section, D.1 (Chevron).

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*Compared to concurrent controls

TABLE 2

Makhteshim Two Year Feeding Study in Rats
#MAK/022/FOL
Selected Neoplastic Findings[a]

Tissue/ Lesion	Sacrif.	DOSE GROUPS (PPM) MALES 0	500	1000	2000	FEMALES 0	500	1000	2000
Thyroid									
C-cell hyperplasia	DOT	2/27	4/20	5/20	0/21	1/13	2/12	2/12	1/9
	Final	3/33	0/1	0/1	4/39	10/47	0/0	0/1	12/51
	Total	5/60	4/21	5/21	4/60	11/60	2/12	2/13	13/60
	(%)	(8.3)	(19.0)	(23.8)	(6.7)	(18.3)	(16.7)	(15.4)	(21.7)
C-cell Adenoma	DOT	1/27	2/20	2/20	0/21	2/13	0/12	1/12	1/9
	Final	5/33	0/1	0/1	2/39	2/47	0/0	1/1	7/51
	Total	6/60	2/21	2/21	2/60	4/60	0/12	2/13	8/60
	(%)	(10)	(9.5)	(9.5)	(3.3)	(6.7)	(0)	(15.4)	(13.3)
Malignant Lymphoma	DOT	0/27	0/20	0/20	1/21	0/13	1/12	2/13	1/9
	Final	0/33	1/40	2/40	1/39	0/47	1/48	0/47	2/51
	Total	0/60	1/60	2/60	2/60	0/60	2/60	2/60	3/60
	(%)	(0)	(3.3)	(3.3)	(3.3)	(0)	(3.3)	(3.3)	(5)
Mammary									
Benign fibro-epithelial	DOT	0/7	0/5	0/5	1/4	2/13	1/12	2/12	2/8
	Final	2/6	1/4	3/4	2/4	5/47	4/8	6/11	10/51
	Total	2/13	1/9	3/9	3/8	7/60	5/20	8/23	12/60
	(%)	(15.4)	(11.1)	(33.3)	(37.5)	(11.7)	(25)	(34.8)	(20)

[a]data excerpted from submitted study. DOT = Died on test/moribund sacrifice.

3. Lifetime Oncogenicity Feeding Study in Mice (Chevron)

Folpet was fed in the diet to 80 male and 80 female Charles River CD-1 mice for 112-113 weeks at 0, 1000, 5000, and 12000 ppm (nominal concentrations). A combined control group of 104 mice/sex (54/control group) was used. This study was conducted at Chevron Environmental Health and Toxicology.

Duodenum - Tumor Incidences are Shown in Table 3.

Adenocarcinomas of the duodenum were significantly increased* at the mid and high dose in both sexes (high dose: 45% in males, 39% in females, vs 0% in controls):

$p \leq 0.01$ in males at mid and high-dose and females at high dose
$p \leq 0.05$ in females at mid-dose.

Adenomas were significantly increased* at the high dose in both sexes ($p \leq 0.01$).

The incidence of neoplasia for both sexes at the high dose was 51% compared to $\leq$ 1% for historical controls [data from Peer Review of Captan].

Dose-related increases in carcinoma incidences in all male treatment groups, and in mid and high dose females, was accompanied by a dose-related increased incidence of mucosal hyperplasia and proliferation of glands in the duodenum.

Stomach - Tumor incidences are shown in Table 4.

Papillomas of the non-glandular stomach were also significantly increased* ($p < 0.01$ by Chi^2 Trend Test [Saunders]) in females (but not in males). (Registrant calculated $p = 0.07$ for high dose by pair-wise comparisons - exact method was not specified).

No other treatment-related effects on the stomach were apparent. It was noted that there was no report of hyperkeratosis/acanthosis, which was of high incidence in the Makhteshim study, to be discussed in the next section.

Historical control data have been requested but not received from Hazleton, however, as far as the duodenal tumors were concerned, it was apparent that the tumors were treatment-related since the incidence in concurrent controls was zero and that in treated animals 40-50%.

The MTD was probably reached at mid-dose as evidenced by a 10% decrease in mean body weight (15% decrease at high-dose). It was noted that tumors occurred not only at the highest dose tested, but at the mid dose, as well.

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*Compared to concurrent controls

DER: Chevron Mouse Oncogenicity
Socal #5-1331

TABLE 3

Duodenum	MALES Con	Low	Mid	High	
Number of Readable Tissues	(87)	(61)	(67)	75 ~~(71)~~	
Number of Animals with Duodenal Neoplasms	1% (1)	3% (2)	12%* (8)	51% ~~54%~~** (38)	← N = 75
Adenoma	1% (1)	2% (1)	3% (2)	14%** (10)	← N = 71
Adenocarcinoma	0%	2% (1)	10%** (7)	45% ~~48%~~** (34)	N = 75
Other Neoplasms	0%	0%	0%	0%	
Mucosal Hyperplasia	3% (3)	33%** (20)	43%** (30)	68%** (49)	N = 71
Duodenum	**FEMALES Con**	**Low**	**Mid**	**High**	
Number of Readable Tissues	(88)	(63)	(67)	74 ~~(73)~~	
Number of Animals with Duodenal Neoplasms	0%	2% (1)	10%** (7)	51% ~~52%~~** (38)	N = 74
Adenoma	0%	2% (1)	4% (3)	18%** (13)	
Adenocarcinoma	0%	0%	.7%* (5)	39% ~~40%~~** (29)	N = 75
Other Neoplasms	0%	2% (1)	0%	1% (1)	
Mucosal Hyperplasia	10% (9)	40%** (25)	41%** (28)	53%** (39)	

*Signigicantly more than controls ($p \leq 0.05$).
**Significantly more than controls ($p \leq 0.01$).

Chevron Mouse Oncogenicity
Socal #s-1331

Summary of the Incidence of Gastric Neoplasia[a]

	MALES (PPM) 0	1000	5000	12000
Number of readable tissues	103	79	80	78
Papilloma	1 (1.0%)	1 (1.3%)	5 (6.3%)	6 (7.7%)
Squamous Cell Carcinoma	0 (0%)	0 (0%)	1 (1.3%)	1 (1.3%)
Mucosal Hyperplasia	12 (11.7%)	19 (24.1%)	2 (2.5%)	10 (12.8%)
Mucosal Hyperplasia (squamous)	0 (0%)	1 (1.3%)	0 (0%)	3 (3.8%)

	FEMALES (PPM) 0	1000	5000	12000
Number of readable tissues	102	79	79	80
Papilloma	1 (1.0%)	4 (5.1%)	5 (6.3%)	1 (1.3%)
Squamous Cell Carcinoma	0 (0%)	1 (1.3%)	0 (0%)	0 (0%)
Mucosal Hyperplasia	4 (3.9%)	5 (6.3%)	3 (3.8%)	3 (3.8%)
Mucosal Hyperplasia (squamous)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[a]data excerpted from submitted study.

4. Lifetime Oncogenicity Feeding Study in Mice (Makhteshim)

Folpet was fed in the diet to 52 male and 52 female Charles River B6C3F1 mice for 21 weeks at 0, 1000, 5000 and 10000 ppm (lowered at week 22 to 0, 1000, 3500 and 7000 ppm due to excessive toxicity (nominal concentrations). Mice were fed for a total of 104 weeks. This study was conducted at Life Sciences' Research, Israel. Tumor incidences are summarized in Table 5.

Duodenum

The major finding at necropsy was neoplasia of the duodenum. Dose-related increases of carcinoma were noted in all treatment groups. The incidence of adenoma of the duodenum was apparently only slight. As in the Chevron study, the incidence of carcinoma was accompanied in all treatment groups by a dose-related increase in the incidence of mucosal hyperplasia and proliferation of glands in the duodenum.

Stomach

In females, but not in males, there was a signigicant increase ($p< 0.05$ by life table trend analysis by investigator) in papilloma of the non-glandular stomach. The combined incidences of papilloma and squamous cell carcinoma in males, although not clearly dose-dependent suggested a possible treatment-related effect. Dose-related increases in the incidence and severity of hyperkeratosis of the esophagus and non-glandular stomach were noted in all treatment groups.

Other sites

In high dose females only, the incidence of malignant lymphoma was statistically significant, however in males at final sacrifice, there was a statistically significant decrease in this finding.

No treatment-related hyperplasia or other toxicity was noted in any lymphoid tissues.

Historical control data have been requested but not received from the Registrant.

NTP has tabulated historical tumor incidences for the B6C3F1 mouse (Haseman et al., 1984):

Adenocarcinoma of the duodenum was reported as 0.7 ± 1.2% for males and 0.1 ± 0.4% for females. Range not calculated

Papilloma of the forestomach was reported as 0.3 ± 0.7% for males and 0.5 ± 0.4% in females. Range not calculated

Squamous cell carcinoma was reported as 0% in males and 0.1% ± 0.4% in females. Range not calculated

Lymphoma was reported as 12.0 ± 7.2% in males (range 2-32% and 25.1 ± 10.0% in females (range 8-62%).

4. Lifetime Oncogenicity Feeding Study in Mice (Makhteshim)

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Stomach

In males, but not in females, there was a signigicant increase ($p < 0.05$ by life table trend analysis by investigator) in papilloma of the non-glandular stomach. The combined incidences of papilloma and squamous cell carcinoma in males, although not clearly dose-dependent suggested a possible treatment-related effect. Dose-related increases in the incidence and severity of hyperkeratosis of the esophagus and non-glandular stomach were noted in all treatment groups.

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TABLE 5

B6C3F1 Mice

Summary of Tumor Incidences for all Animals on Test

	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
	%	%	%	%	%	%	%	%
Adenoma	0	1.9	0	4	2.1	2	9.8	2.1
Duodenal Carcinoma	0	5.7	32	44	0	2	9.8	38.3
Papilloma of non-glandular stomach	0	3.8	5.8	3.8	3.9	1.9	9.6	13.5
Squamous cell carcinoma of the stomach	0	0	5.8	1.9	0	1.9	0	0
Malignant Lymphoma	25	21.2	23.1	17.3	30.7	30.7	36.5	50.0

The incidences of all tumor types (except lymphoma) found in treated animals exceeded that in corresponding NTP historical controls.

MTD is an issue with this study, since it appears to have been exceeded at the high dose* as evidenced by decreases in body weight of 25%, however, an oncogenic response was seen here at all dose levels.

*The registrant's investigators calculated a reduced "probability" of survival of all treated males, and mid and high dose females. However, relative to other studies reviewed in Tox Branch, overall survival in this study was unusually high in all test groups [S. Saunders]).

E. Additional Toxicology Data on Folpet:

1. Metabolism:

Folpet rapidly degrades to phthalimide in the presence of human blood in vitro, with an estimated half-life of about 1 minute. The proposed mechanism of folpet toxicity suggests that folpet spontaneously degrades at neutral or alkaline pH to yield phthalimide and thiophosgene radicals, which are apparently efficiently scavenged by glutathione and other sulfhydryl compounds. It is presumed, therefore that little, if any, folpet (unchanged) is absorbed systemically, since the trichloromethylthio- side chain is very labile in the presence of sulfhydryls at neutral or alkaline pH. The small amount of folpet thought to be absorbed is probably rapidly degraded.

A proposed reaction pathway for thiophosgene, an active metabolite common to both folpet and captan, is shown in Figure I. Thiophosgene is a highly reactive intermediate which can bind non-enzymatically to sulfhydryls and/or tissue macromolecules.

The phthalimide backbone of Folpet has an unsaturated benzene ring. Captan, unlike folpet, has a partially saturated ring structure (tetrahydro/phthalimide). The metabolic pathways for captan are shown in Figure II. By analogy to the known metabolic pathways of captan, and other unsaturated benzene ring-containing compounds, the formation of phenols and dihydrodiols via epoxide intermediates can be inferred for folpet.

There are no mammalian metabolism data for folpet available in Agency files.

FIGURE I

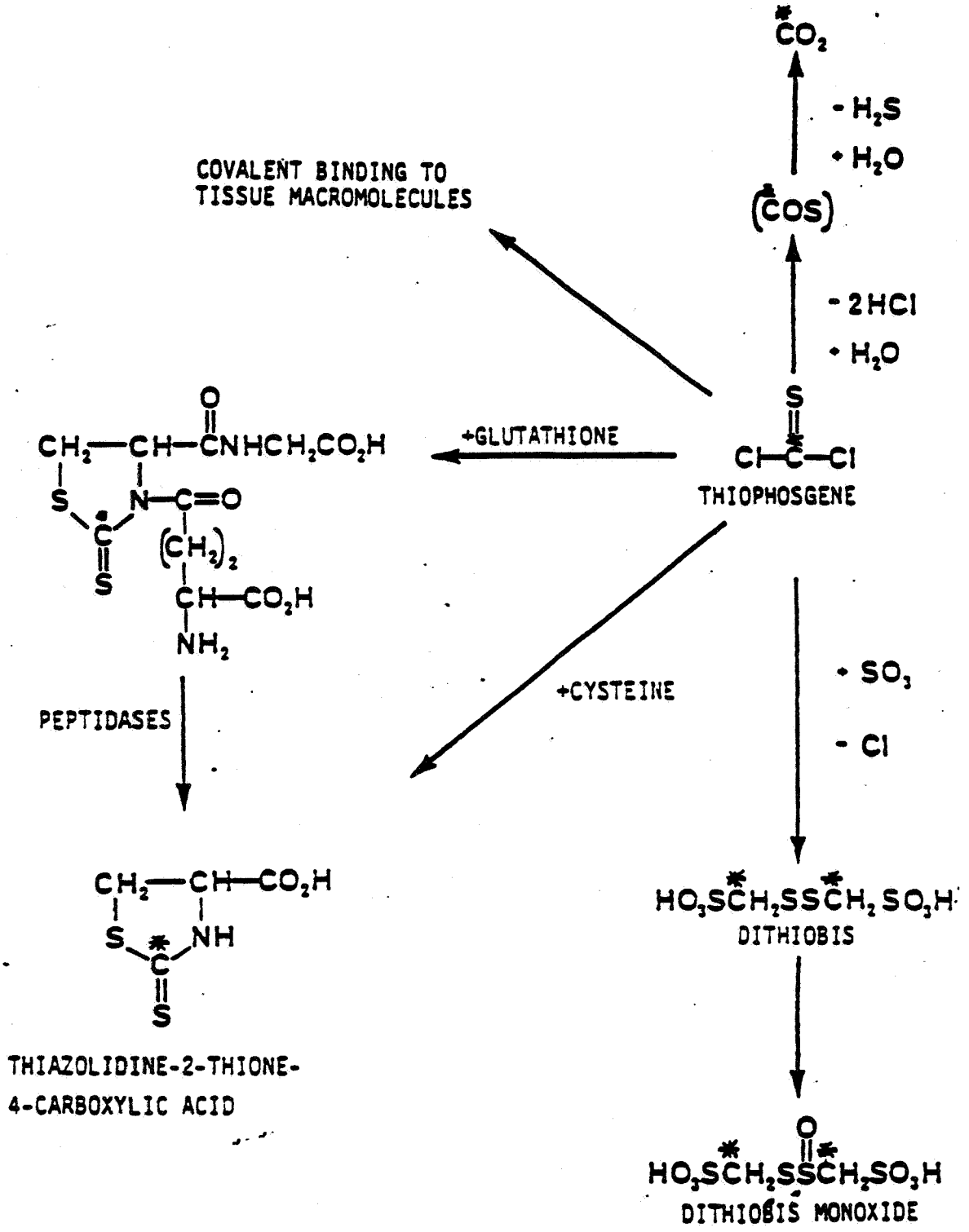
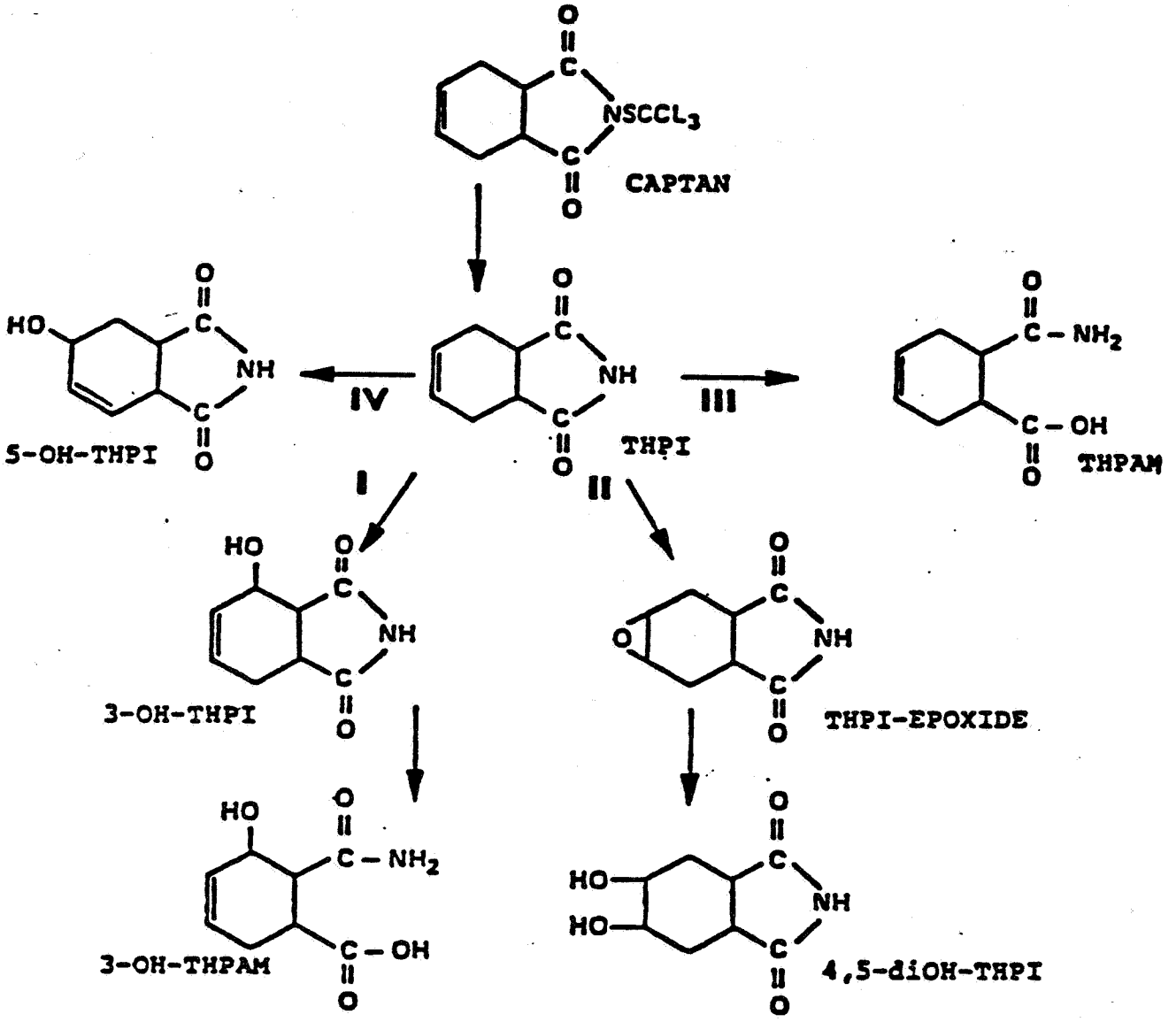


Figure 1. Proposed Fate of Thiophosgene ($\overset{*}{C} = {}^{14}C$).

From: Dynamac Special Report on Folpet.

FIGURE II


NSCCl3
CAPTAN
HO
NH
5-OH-THPI
IV
NH
THPI
III
C – NH2
C – OH
THPAM
I
II
HO
NH
3-OH-THPI
O
NH
THPI-EPOXIDE
HO
C – NH2
C – OH
3-OH-THPAM
HO
HO
NH
4,5-diOH-THPI

2. Non-Oncogenic Toxicological Effects

Folpet is not very acutely toxic: LD_{50} = 20-40 g/Kg in the rat, and 2.5 g/Kg in the mouse. It is not a primary skin irritant, but it is a moderate eye irritant and has skin sensitizing properties. Folpet cross-reacts with captan as a skin sensitizer.

Folpet has been demonstrated to be teratogenic in the rabbit (hydrocephalus) under standard protocols, but not with "pulse-dose" protocol. Folpet was negative for teratogenicity in the rat. Possible teratogenic findings, reported in a screen test (Kotin, Falk, et al. 1968), have not been fully characterized for the mouse.

In the "mouse-spot test" a significant decrease in pup survival over 28 days of lactation was observed in all treatment groups.

3. Mutagenicity:

Folpet has been show to be mutagenic in vitro in bacteria, yeast, and mammalian systems. Mutagenic activity of Folpet is usually reduced by the addition of S-9 or other free sulfhydryl-containing mixtures.

Folpet is positive in:

Gene Mutations

Salmonella TA100, TA1535, TA1538
E. coli WP2
Mouse Lymphoma L5178Y TK+/-
Drosophila sex-linked recessive

DNA Repair

Bacillus subtilis rec+/-
E. coli pol A+/-
Unscheduled DNA synthesis (WI-38 fibroblasts)
Mitotic Recombination (Saccharomyces)

Folpet is negative in the following in vivo assays:

Chromosome Aberrations

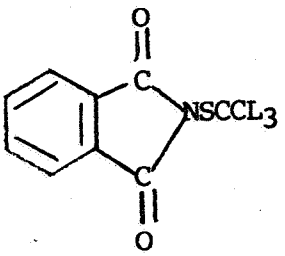
Mouse Dominant Lethal
Rat Bone Marrow Cytogenetics

Other

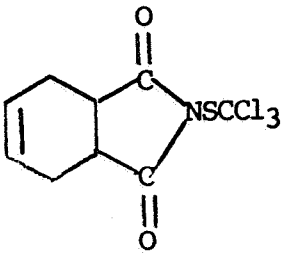
Mouse somatic cell mutation assay (negative for mutations - however significant pup mortality noted at low doses.)

4. Structure-Activity Correlations:

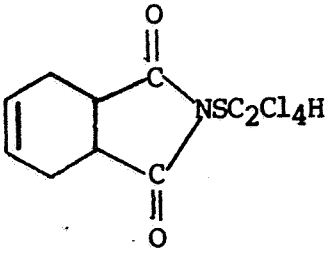
Folpet is structurally similar to captan and captafol (both also fungicides).



FOLPET



CAPTAN



CAPTAFOL

Captan, which structurally is more similar (than captafol) to folpet, has been shown to produce duodenal tumors in 2 mouse strains: CD-1 and B6C3F1. Captan has been evaluated in Peer Review as a Category B2 carcinogen.

Both captan and captafol are associated with a slight increase in renal tumors in the Charles River CD rat, and both are mutagenic in a number of test systems.

F. Weight of Evidence Considerations:

The committee considered the following facts regarding toxicology data on folpet to be of importance in a weight of evidence determination of oncogenic potential.

Feeding of folpet in the diet is associated with the following:

MOUSE

1. Chevron Study

Treated Charles River CD-1 mice had a statistically significant increased incidence over the controls of the following tumors:

°Duodenal adenocarcinoma in males at mid and high dose and in females at high doe.

°Duodenal adenomas at high dose in both sexes

°Duodenal neoplasms at mid and high dose in both sexes (50% at HDT in both sexes) and

°Papilloma of the stomach in high dose males.

WOE - Mouse (contd.)

2. Makhteshim Study

Treated Charles River B6C3F1 mice had a dose-related increase in carcinoma of the duodenum at all doses in females, and in mid and high dose males - and:

°Increases in duodenal adenoma in high dose males and mid-dose females

°Statistically significant increases in the incidence of papilloma of the non-glandular stomach in females. In males the combined incidence of squamous cell carcinoma and papillomas suggests a possible treatment-related effect.

°Dose-related increased incidence and severity of hyperkeratosis of the esophagus and non-glandular stomach in all treatment groups.

°A statistically significant increase in the incidence of malignant lymphoma in high dose females, however in males there was a statistically significant <u>decrease</u> in the finding at final sacrifice.

°MTD was apparently exceeded at high dose, however since tumors were seen even at mid dose and the findings here were so similar to the Chevron study, the Committee did not disqualify this study.

<u>RAT</u>

3. Data from 2 rat studies were also examined:

1) Chevron: Spraque Dawley 2)Makhteshim: Fischer 344

These studies showed apparently equivocal responses in thyroid C-cell neoplasia in that they occurred in the <u>male</u> SD rat and in the <u>female</u> F344 rat.

°In the SD rat there were also increases in testicular interstitial cell neoplasia.

°Treatment-related increases in the incidence of hyperkeratosis/acanthosis occurred in mid and high dose males and females. These could be considered "preconditional" to neoplasia [L.Kasza], and were of serious concern, since in the Makhteshim mouse study these lesions were also accompanied by papillomas. Moreover, for both rat studies, it appears that an MTD was not used.

The Committee agreed to withhold judgement on the rat studies until more data is received ie: historical control data from the 2 laboratories; and for completion of the formal review of the Makhteshim (F344 rat) study.

4. Captan, a structural analog of folpet, also induced a high incidence of duodenal neoplasms in the mouse.

5. Folpet is mutagenic in a number of <u>in vitro</u> test systems.

G. Classification of Oncogenic Potential:

Criteria contained in the proposed EPA Guidelines [Draft Jan.7, 1986] for classifying a carcinogen were considered. These Guidelines state that -

For Group B - Probable Human Carcinogen:

"Sufficient evidence of carcinogenicity .... indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors:

a) in multiple species or strains [MET] ; or
b) in multiple experiments (e.g., with different routes of administration or using different dose levels); or
c) to an unusual degree in a single experiment with regard to high incidence [MET], unusual site or type of tumor [MET], or early age at onset.

Additional evidence may be provided by data on dose-response effects [MET], as well as information from short-term tests [MET] or on chemical structure [MET]".

B1 = "... limited evidence of carcinogenicity from epidemiology studies.."
B2 = "... inadequate evidence or no data from epidemiology studies..."

The Committee agreed that the evidence for carcinogenicity of folpet was strong in the mouse, in which it induced carcinoma and adenoma of the duodenum (relatively unusual site) in 2 strains. Based on this evidence alone, parts a) and c) of the above criteria for Group B are met. Additional supporting evidence was provided from short-term tests (folpet was mutagenic in several in vitro assays) and structure-activity relationships (SAR) (folpet is a structural analog of captan, which also induces duodenal carcinoma in the mouse.

Thus folpet meets 2 of the criteria for Group B, any one of which alone can be sufficient for such a classification; SAR and mutagenicity provide additional supporting evidence.

Although the rat studies were considered inadequate at this time, the finding of some "preconditional" lesions seen in the mouse (hyperkeratosis/ acanthosis) was considered significant, particularly since the dosing regimen in rats did not appear to have reached a MTD.

The Committee concluded that the available data for folpet in animals is "Sufficient evidence for carcinogenicity" and classified it as a B2 "Probable Human Carcinogen" (there is no available data from epidemiology studies).